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Green synthesis of new hippuric hydrazones

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ABSTRACT

Hippuric hydrazones **4–8** were prepared starting from treating the corresponding acid with ethanolic HCl forming the corresponding ester **2**. The formed ester was then converted to ethyl hippurate **3** by treating the ester with hydrazine hydrate. The formed ethyl hippurate was then irradiated with various substituted aromatic aldehydes under solvent-free conditions forming new series of hippuric hydrazones **4–8**. Developing clean synthetic route for synthesizing hippuric hydrazones is the main point of this work which is environmentally and economically desirable. The synthesized compounds were confirmed by spectral NMR, mass, IR and CHN analysis data.

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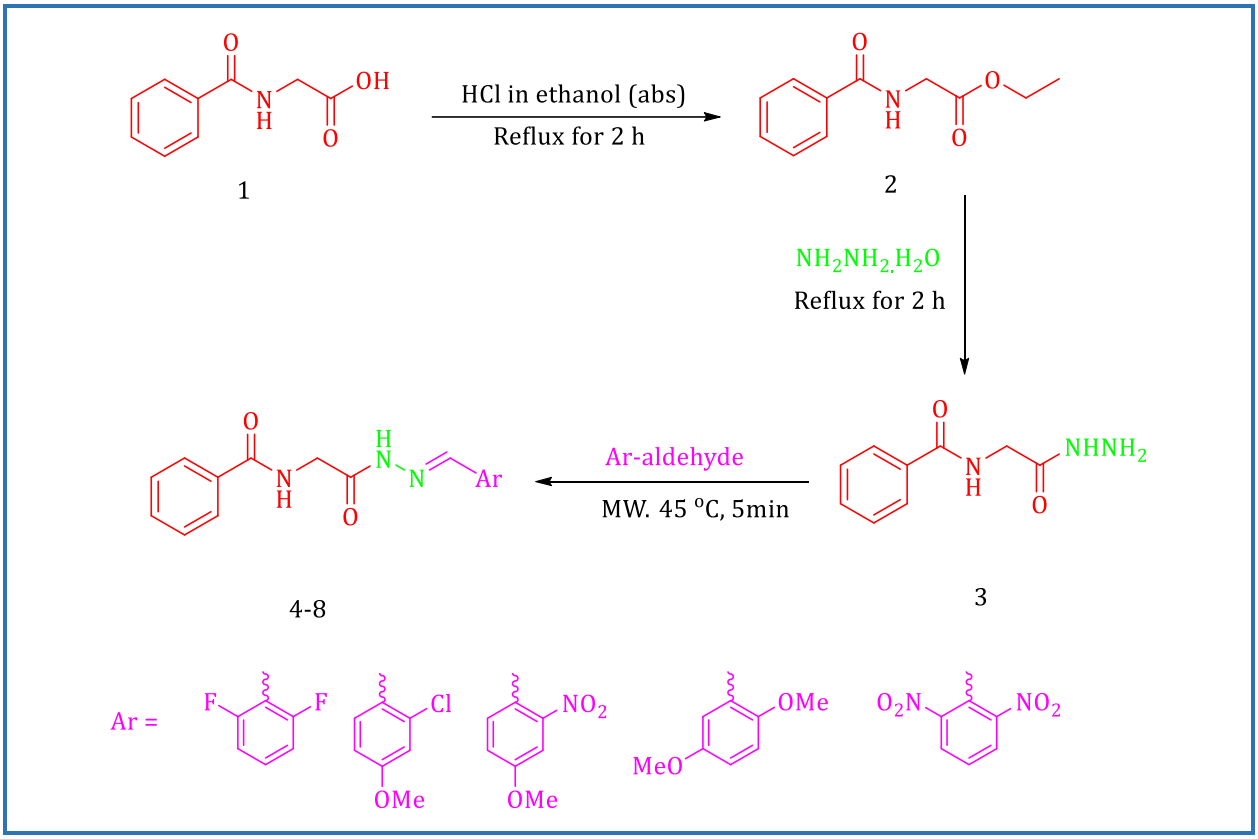
Graphical Abstract



Introduction

Hydrazone is a compound that consist of the moiety $R_1R_2C=N-NH_2$. The existence of this moiety in the structure of hydrazone plays a significant key role in the chemistry of organic compounds [1–7]. Hydrazones have been confirmed to possess significant biological activities for instants anti-HIV [8, 9], anti-prion activities [10], antituberculous [11], anti-inflammatory [12], antioxidant [13], antimalarial [14] and anticonvulsant [15]. A wide range of aldehydes and ketones can be heated with appropriate hydrazines/hydrazide using protic solvents such as methanol, ethanol and glacial acetic acid forming hydrazones [16, 17]. The reactivity of hydrazones toward electrophiles and nuclophiles can be regarded as their significant features. In this sense, they can be used for synthesizing different kinds of heterocyclic compounds [18]. It was reported that hydrazides were discovered to possess considerable biological characteristics towards certain diseases [19], thus changing these compounds into their corresponding hydrazones rise the bio-activities of these compounds according to the well-known C=N activity [20]. Moreover, it was reported that these compounds shows physiological activities in the therapy of diseases; such as tuberculosis [21–23]. Hydrazones in analytical chemistry acts as multidentate ligands for transition metals in colorimetric and

fluorimetric determinations [24, 25]. It has been reported that hippuric acid possesses significant biological activities against certain diseases [26]. Therefore, here we synthesized a new set of hydrazones with the moiety of hippuric acid using microwave method as a green and efficient method which is environmentally and economically desirable and is valuable in anti-prion agent which is the subject our next work.

Experimental

Materials and methods

All reagents were used without further purification and purchased from commercial sources. Melting point measurements were recorded using Gallenkamp machine. Smith CreatorTM Optimiser EXP reaction was used for microwave reactions. Bruker AV-1400 model NMR instrument, 400 MHz was used for ^{1}H NMR analysis. Water-Micromass LCT electrospray mass spectrometer was used for accurate masses measurements. CHN analysis was carried out using a Perkin Elmer 2400 series II CHN analysis. All reactions and measurements were carried out at Sheffield university/ department of chemistry/ Great Britain. Ethyl hippurate **2** was prepared following the reported procedure [27]. Hippuric hydrazide **3** was synthesized following the published procedure [28].

*Microwave synthesis of hippuric hydrazones **4–8***

An equimolar quantity of hydrazide **3** and substituted benzaldehyde were mixed in a microwave vial 20 mL. The mixture was irradiated and heated up to 45 °C (17 bar) for five minutes and then cooled to 25 °C. Subsequently, an ice-cold water was added slowly to the mixture. A precipitate was formed, collected and purified by recrystallization from ethanol-water (1:1) providing the pure product as a white crystal compound**,** (Scheme 1).

*(E)-N-(2-(2-(2,6-difluorobenzylidene)hydrazinyl)-2-oxoethyl)benzamide **(4)***

White crystal, mp 159−160 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3420 (NH), 3213 (NH), 3060 (Ar-CH), 2916 (aliphatic-CH), 1697, 1637 (C=O), 1624 (C=N), 1595, 1481 (C=C), 1430 (C-H), and 1367 (C-N). ^{1}H NMR (DMSO-d_6): δ 12.2 (bs, 1H, NH), 8.2 (s, 1H, NH), 8.4-7.4 (m, 7 Ar-H), (s, 1H, CH), 5.5, 5.2 (s, 2H, CH_2 in and out of the plane). Anal. Calculated for $C_{16}H_{13}F_2N_3O_2$: C, 57.66; H, 3.93; N, 12.61; F, 11.40 Found: C, 57.40; H, 3.63; N, 12.51; F, 11.26.

*(E)-N-(2-(2-(2-chloro-4-methoxybenzylidene)hydrazinyl)-2-oxoethyl)benzamide **(5)***

White crystal, mp 150 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3189 (NH), 3064 (NH), 3066 (Ar-CH), 2863 (aliphatic-CH), 1697, 1628 (C=O), 1610 (C=N), 1562, 1442 (C=C), 1382 (C-H bend), and 1356 (C-N). ^{1}H NMR (DMSO-d_6): *δ* 11.9 (bs, 1H, NH), 8.3-6.6 (m, 7 Ar-H), (s, 1H, CH), 5.6, 5.2 (s, 2H, CH_2 in and out of the plane), 3.7 (s, 1H, NH), 3.8 (s, 3H, OCH_3). Anal. Calculated for $C_{17}H_{16}ClN_3O_3$: C, 56.44; H, 4.46; Cl, 9.80; N, 11.61. Found: C, 56.32; H, 4.41; N, 11.52.

(E)-N-(2-(2-(4-methoxy-2-nitrobenzylidene)hydrazinyl)-2-oxoethyl)benzamide ***(6)***

White crystal, mp 146 °C, IR (KBr) (ν_{max}/ cm^{-1}): 2962 (NH), 2900 (NH), 3074 (Ar-CH), 2962 (aliphatic-CH), 1682, 1629 (C=O), 1608 (C=N), 1576, 1415 (C=C), 1396 (C-H bend), 1352 (C-N). ^{1}H NMR (DMSO-d_6): *δ* 12.0 (bs, 1H, NH), 8.2 (s, 1H, NH), 8.3-7.4 (m, 7 Ar-H), (s, 1H, CH), 5.6, 5.2 (s, 2H, CH_2 in and out of the plane), 3.9 (s, 3H, OCH_3). Anal. Calculated for $C_{17}H_{16}N_4O_5$: C, 54.84; H, 4.33; N, 15.05; Found: C, 54.79; H, 4.27; N, 14.78.

(E)-N-(2-(2-(2,5-dimethoxybenzylidene)hydrazinyl)-2-oxoethyl)benzamide ***(7)***

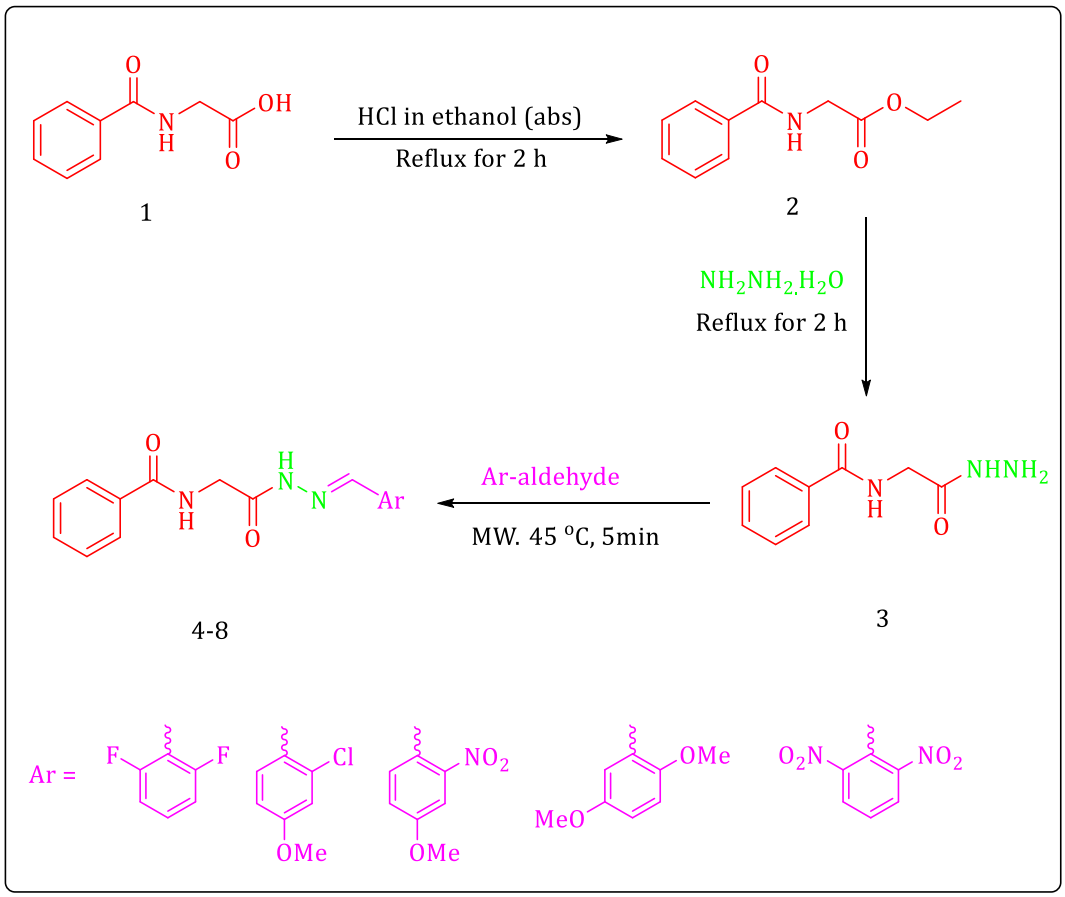
White crystal, mp 152 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3182 (NH), 3073 (NH), 3063 (Ar-CH), 2959 (aliphatic-CH), 1701, 1667 (C=O), 1614 (C=N), 1582, 1416 (C=C), 1392 (C-H bend), 1332 (C-N). ^{1}H NMR (DMSO-d_6): *δ* 11.8 (bs, 1H, NH), 8.3-7.0 (m, 7 Ar-H), (s, 1H, CH), 5.6, 5.2 (s, 2H, CH_2 in and out of the plane), 3.7 (s, 1H, NH), 3.8 (s, 6H, $(OCH_3)_2$). Anal. Calculated for $C_{18}H_{19}N_3O_4$: C, 60.50; H, 5.36; N, 11.76; Found: C, 60.46; H, 5.23; N, 11.69.

(E)-N-(2-(2-(2,6-dinitrobenzylidene)hydrazinyl)-2-oxoethyl)benzamide ***(8)***

White crystal, mp 152 °C, IR (KBr) (ν_{max}/ cm^{-1}): 3205 (NH), 3160 (NH), 3075-3026 (Ar-CH), 2965 (aliphatic-CH), 1682, 1644 (C=O), 1601 (C=N), 1576, 1486 (C=C), 1435 (C-H bend), 1395 (C-N). ^{1}H NMR (DMSO-d_6), *δ* 12.1 (bs, 1H, NH), 8.5-7.3 (m, 7 Ar-H), (s, 1H, CH), 5.5, 5.2 (s, 2H, CH_2 in and out of the plane), 3.7 (s, 1H, NH). Anal. Calculated for $C_{16}H_{13}N_5O_6$: C, 49.62; H, 3.38; N, 18.08; Found: C, 49.42; H, 3.31; N, 18.87.

Results and Discussion

In continuation of our interest in the development of green organic synthesis, new series of hippuric hydrazones were synthesized using microwave irradiation as a simple and efficient protocol. This protocol includes irradiating the reaction mixture at 45 °C (17 bar) for five minutes under solvent-free conditions. The reaction progress was followed by TLC check. The product was achieved in an excellent yield within only 5 minutes as compared to the traditional batch method using ethanol as the reaction media, Table 1.



Scheme 1.

From the results above it is noticeable that applying the reaction using the microwave irradiation and under solvent-free condition provides 90-94% of the pure products. On the other hand, only 64-68% of the pure products were obtained when the reaction accomplished using the traditional batch method.

The use of solvent for the synthesis of this series of hippuric hydrazones was also examined. In the microwave method it was observed that using ethanol as a reaction media yielding up to 61 % of the pure product within 5 minutes when the reaction temperature was set at 45 °C (17 bar). The reaction was repeated one more time and rising the temperature up to 50 °C (20 bar). It was observed that a slight diminished in the product yield was found. To obtain the best conditions, the reaction was repeated several times. It was observed that the best optimal condition was performing the reaction in solvent-free condition which also produced better percentage yield of the pure product as compared to the obtained results when using ethanol as a solvent media in the same protocol. This new synthetic route of hydrazones was found to be environmentally and economically desirable.

Table 1. Batch and microwave conditions for hippuric hydrazones **4–8**

Compound	Batch yield %	Batch time/h	Microwave yield %	Microwave time/ min
4	68	3	91	5
5	66	3	90	5
6	65	3	94	5
7	65	3	92	5
8	64	3	90	5

Conclusions

In this work we reported solvent free and ecofriendly synthesis of new series of hippuric hydrazones under microwave condition. It is noticeable that synthesizing this series of hydrazones under solvent-free conditions using microwave irradiation protocol was observed to be the most suitable and optimal reaction protocol which produced high percentage yield of the pure product with shorter reaction time as compared to the conventional batch protocol in the presence of ethanol as a reaction media. Our next work is to investigate the synthesized compounds which may have medical applications particularly as anti-prion diseases agents.

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